tests. It has been used successfully to stimulate the immune system of patients with T-cell–mediated immunodeficiency disorders, such as common variable immunodeficiency and mucocutaneous candidiasis. Cimetidine also augments the clearance of atopic dermatitis and of chronic herpes zoster in immunocompromised patients and reverses the cutaneous anergy of Crohn's disease.

In an uncontrolled, open-label trial, 32 children had multiple recalcitrant common or plantar warts and were treated with cimetidine at a dosage of 25 to 40 mg per kg per day. Although improvement was not noted within the first month of therapy, at six to seven weeks, warts began to disappear. By two months, the warts had disappeared in 26 of the children (81%), with the response rate being higher in the dosing range of 30 to 40 mg per kg per day. No side effects were noted in any patient, and the warts did not tend to recur after the response to cimetidine. In an open-label prospective trial in adults, the clearance of recalcitrant warts was noted in 12 of 18 adults (67%) after three months of cimetidine therapy at a dosage of 30 to 40 mg per kg per day. Others used 1.2 grams per day of cimetidine in six patients with flat warts that had not responded to dinitrochlorobenzene immunotherapy. Four of the six cleared entirely after four weeks of treatment. A double-blind, placebo-controlled trial in children has not been done. A clearance rate of only 31% was recently noted in cimetidine-treated adults with warts, a rate not significantly different from the placebo-treated patients, but much lower than the response rate in the open-label studies in pediatric and adult patients. Further double-blind, placebo-controlled trials are needed to determine efficacy.

Although cimetidine is not approved for use in children younger than 16 years, the medication is used frequently in children with peptic ulcers and by dermatologists for urticaria, mastocytosis, and atopic dermatitis. Side effects are rare, but nausea, vomiting, diarrhea, behavioral changes, and in adolescent boys, gynecomastia have been reported. It is important to remember that cimetidine may interact with two medications commonly used in children, theophylline and phenytoin.

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New Strategies in the Management of Onychomycosis

UNTIL RECENTLY the mainstay of oral therapy for onychomycosis was griseofulvin. This compound was introduced in 1958 and was the first important oral antifungal agent available to treat dermatomycoses. After 35 years, griseofulvin is still an effective agent in the treatment of some dermatomycoses such as tinea capitis. In the treatment of pedal onychomycosis, however, typical response rates were in the order of 20% after 9 to 12 months of therapy, with relapse rates of approximately 40%. This resulted in poor compliance, and in some cases the physician or patient decided against oral therapy, given the relative ineffectiveness of available therapy.

Itraconazole, a triazole antifungal agent, has been recently approved for the treatment of dermatophyte onychomycosis in the United States. The drug is detected in the distal end of the nail plate within 7 to 14 days of starting therapy, reaching the nail plate by diffusion from both the nail bed and nail matrix. Griseofulvin is thought to enter the nail plate through the matrix region only. Following therapy with itraconazole, 200 mg per day for seven days, the drug remains in fingernails and toenails for six and nine months, respectively, after its discontinuation. Itraconazole is present at almost undetectable levels within 10 to 14 days of discontinuing treatment. With griseofulvin, the drug leaves the plasma within days of stopping therapy, and it is likely that levels in the nail plate parallel those in the plasma. Thus, griseofulvin has to be administered for a duration of 9 to 18 months while the diseased toenail is growing outward.

The favorable pharmacokinetics of itraconazole enable the drug to be administered as continuous therapy, 200 mg per day for three months, in the treatment of pedal dermatophyte onychomycosis. Pulse therapy is likely to supersede continuous therapy and is administered at three pulses of 200 mg twice a day (400 mg per day) for one week a month for three consecutive months for pedal onychomycosis. Itraconazole has a broad spectrum of activity and is effective not only against dermatophytes but also in onychomycosis due to *Candida* species and some nondermatophyte molds. The incidence of adverse effects is about 10%, with the most common being gastrointestinal disturbance, cutaneous eruption, headaches, and dizziness. The incidence of asymptomatic elevation of liver function test levels is 1% to 3%. Several drug interactions may occur with itraconazole, and a careful history of other medical conditions and concurrent medications should be obtained.

Terbinafine is an allylamine that has just been approved in the United States for the management of onychomycosis. As with itraconazole, it reaches the nail plate by both the nail matrix and the nail bed and remains in the nail plate for several months once therapy is stopped. It is effective in the treatment of dermatophyte onychomycosis, with the recommended dosage for toenail onychomycosis being continuous therapy with 250 mg per day for 12 weeks.

Limited information is available for fluconazole in the treatment of onychomycosis. This agent is more hydrophilic than itraconazole, and in published studies a dosage regimen is 150 mg once a week for about nine months.

Some topical agents that are used in Europe are amorolfine 5% lacquer, bifonazole with 40% urea paste, 8% ciclopirox nail lacquer, and 28% tioconazole. These are generally not effective when onychomycosis involves a substantial portion of the nail or when the matrix is in-

volved. In some studies, topical agents have complemented oral therapies. Chemical nail avulsion or surgical measures are more likely to be used in Europe, and in appropriate instances may be adjuncts to oral treatment.

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